REMARKS

Claims 1-21, 43-46 and 48-64 are pending. Applicants thank the Examiner for rejoining claims 17-21 as directed to a process of using the product including the limitations of the product recited in claims 1-16 and 40-50. Claims 1-2, 8-10, 12, 13, 43-46 and 48-50 have been amended in response to the Examiner's objections, to correct errors or to clarify the subject matter claimed. Claims 40-42 and 47 have been canceled. New claims 51-64 have been added. Applicant reserves the right to prosecute any withdrawn or cancelled subject matter in one or more continuation or divisional applications.

The Examiner has objected to claims 43 and 48 as improperly depending from a canceled claim. Claim 43 and 48 have been amended to correct this error.

The Examiner has also objected to the specification for including an embedded hyperlink as well as for including certain inappropriate characters. The specification has been amended to address these objections.

REJECTION UNDER 35 U.S.C. §101

The Examiner has rejected pending claims 1-16 and 40-46 under 35 U.S.C. §101 as claiming non-statutory subject matter. Applicants note that claims 40-42 have been canceled solely in the interest of promoting prosecution. The rejections are addressed below for the remaining claims.

The Examiner asserts that pigs lacking any expression of functional α(1,3)galactosyltransferase ("α(1,3)GT") can be naturally occurring. Applicant notes that pigs that possess two inactive alleles of the α(1,3)GT gene are not found in nature. The fact that α(1,3)GT null pigs are not naturally occurring is described in the specification (for example on page 10, lines 12-14, page 15, lines 20-21). Nevertheless, to clarify that the Applicant does not intend to claim non-statutory subject matter, but instead, that the Applicant's invention requires human intervention, the claims have been amended to recite that the pig be "non-naturally occurring". This amendment finds support, for example, on the above-referenced pages.

The Examiner has also rejected pending claims 43-46 under 35 U.S.C. §101 because the claims could be interpreted to encompass humans. The claims have been amended to recite a non-naturally occurring *pig* produced by a method of claim 17, 18, 19, 20 or 21.

Applicants believe that these amendments overcome the Examiner's rejections.

REJECTION UNDER 35 U.S.C. §102(B)

The Examiner has rejected claims 8, 13, 40, 42 and 47-50 under 35 U.S.C. §102(b) over Gustafsson et al. (U.S. Patent No. 6,153,428). The Examiner asserts that Gustafsson teaches cells and tissues of a pig that lacks expression of functional α(1,3)GT. As noted above, claims 40, 42 and 47 have been canceled.

Applicant disagree that Gustafsson teaches any tissues or cells from a pig that lacks expression of functional α(1,3)GT, as recited in the pending claims. The present invention is based on the first successful birth of viable pigs that lack any expression of functional α(1,3)GT. Despite the fact that the production of alpha 1,3 gal null pigs has been a goal in the field of xenotransplantation for decades, as noted in the specification, a homozygous α(1,3)GT knock out pig was not produced until 2002, as part of the present invention (see pages 5-6). This feat was published in *Science* in January, 2003 by Phelps *et al.* (Phelps, et al. *Science* 299 (5605) 411 (January 17, 2003)). The Phelps discovery was heralded as a breakthrough in the xenotransplanation literature.

In contrast, Gustafsson is one of any number of publications and patent application that simply discuss the desired production of α(1,3)GT negative cells and animals. Gustafsson articulates a desired result, a hoped-for discovery that was well documented in the scientific literature in at the time (1994). Gustafsson does not disclose or suggest the tissues or cells of the amended claims because no one would have been able to produce the claimed pigs based on these statements.

Gustafsson does include prophetic example for making a swine null for α(1,3)GT. In that example (Example 6), Gustafsson suggests using porcine embryonic stem cell cultures to produce the animals. This suggestion underscores the point that Gustafsson clearly expresses only a hoped-for result. At the time Gustafsson was filed those skilled in the art assumed that it would be a simple feat to produce large animals based on the same principles as used in creating knock-out mice, i.e., using embryonic stem cells. Yet, unlike mice, embryonic pig stem cells have not been useful to produce transgenic animals. The same options for genetic modification (i.e. gene targeting) that are available for mice have proven inapplicable to larger animals, like

pigs (see Denning and Priddle (2003) *Reproduction* 126:1-11, published after the filing date of the present invention, for review, "[u]ntil recently, precise modification of the animal genome by gene targeting was restricted to the mouse because germline competent embryonic stem cells are not available in any other mammalian species." (abst)). Put another way, one could not have produced a pig with functional inactivation of α(1,3)GT following the teaching of Gustafsson, at the time or even today.

In fact, while Gustafsson was filed in 1994, it was not until 1996 that a technology existed to allow the cloning of large animals. The first cloning of a mammal animal from established adult somatic cells, well known as "Dolly" the sheep, was reported in 1996, two years after the priority date of the Gustafsson patent (Campbell KH, McWhir J, Ritchie WA, Wilmut I. "Sheep cloned by nuclear transfer from a cultured cell line." *Nature.* 1996 Mar 7;380(6569):64-6). As the Examiner is well aware, the cloning of Dolly was heralded as a scientific breakthrough and well outside the skill of even an expert, let alone a person of ordinary skill in the art. The first cloned pig did not exist until a full six years after Gustafsson's filing, and four years after the cloning of Dolly (see Polejaeva IA, et al. (2000) Nature. 407:86-90).

Therefore, there is no teaching in Gustafsson that would have enabled anyone to produce the animals prophetically disclosed. Indeed the techniques to do so were not even developed until years after Gustafsson's filing date. Thus, without the ability to produce pigs lacking any expression of alpha-1,3-GT, Gustafsson does not anticipate the pending claims.

The Examiner also rejected claims 1-16, 40, 42-44 and 46-49 under 35 U.S.C. §102(e) as anticipated by Denning et al. (U.S. Patent No. 7,126,039). As noted above, claims 40, 42 and 47 have been canceled. The Examiner alleges that Denning teaches a pig, its organs, tissues and cells that lack expression of an α(1,3) Gal gene. The Denning reference, similar to Gustafsson merely discusses the desired production of alpha-1,-3GT null pigs. And, like Gustafsson, fails to teach the cells and tissue of the present invention. Moreover, the Denning specification and examples are directed almost exclusively to sheep. The only examples that are described as having been reduced to practice are for sheep cells, Example 4 describes the production of a sheep cells heterozygous for the alpha-1,3-GT gene. Further, there is no example in Denning showing that any transgenic animal was actually produced.

Prior to this invention, no one knew whether the disruption of both alleles of the alpha-1,3-GT gene would be lethal or would effect porcine development or result in an altered phenotype (Ayares et al. Graft 4(1)80-85 (2001); Sharma et al. Transplantation 75:430-436 (2003); Porter & Dallman Transplantation 64:1227-1235 (1997); Galili, U. Biochimie 83:557-563 (2001)). Indeed, many experts in the field expressed serious doubts as to whether homozygous alpha-1,3-GT knockout pigs would be viable at all, much less develop normally (see pages 7-8 of the specification). Such concerns were expressed up until the double knockout of the present invention was produced.

By providing only a prophetic example based on a technique that would not be expected to succeed, neither Denning nor Gustafsson have overcome the reasonable expectation of failure that was apparent in the art. One of skill in the art reading Denning or Gustafsson would have interpreted the specification as merely a suggestion that a homozygous α(1,3)GT null mutant produced by homologous recombination would be desirable. However, they were not taught any ways to produce a viable null mutant. In essence, both Denning and Gustafsson merely direct others to experiment using complex techniques without providing any guidance that would be expected to produce success.

The references cited by the Examiner each provide a mere suggestion that a pig lacking functional α(1,3)Gal would be desirable. However, at the time of filing, *no one* had produced a pig lacking expression of functional α(1,3) Gal, or even a homozygous knock-out cell in culture. The techniques that were known in the art were extremely difficult and success using these was well beyond the reach of the ordinary artisan. Further, the teaching in the art suggested that attempts to produce such animals would run into a number of viability issues.

REJECTION UNDER 35 U.S.C. §112

The Examiner has rejected claims 17-21 and 43-50 under 35 U.S.C. §112, first paragraph as not enabled for a method of producing pigs by embryonic stem cell technology or to produce other, non-porcine animals by nuclear transfer technology. Without agreeing with the Examiner, Applicants have amended claims 43-50 to recite a 'pig', thus rendering the Examiner's second objection moot.

Applicants are unclear as to the basis for the Examiner's rejection of claims 17-21. As the Examiner notes, these claims are directed to "A method ... comprising: breeding a male pig heterozygous for the alpha-1,3-GT gene with a female pig heterozygous for the alpha-1,3-GT gene." The Examiner asserts that these claims "embrace a pig produced by embryonic cell knock out technology."

Applicants note that the present Applicants actually showed the production of cloned pigs from homozygous fetal fibroblasts and the breeding of two heterozygous pigs to produce homozygous knockouts (Example 6). This is what Applicants understand to be the plain reading of this claim. If the Examiner believes otherwise, Applicants request that the Examiner contact Applicants' representative to clarify this objection.

The Examiner has also rejected claim 47 under 35 U.S.C. §112, second paragraph for lack of antecedent basis for the term "animal". Applicants have amended the claim to correct this.

Applicants believe no additional fees are required with this response. Should the Examiner determine otherwise, the Commissioner is authorized to charge any underpayment of fees to Deposit Account No. 11-0980.

Respectfully submitted,

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